

The pending claims are directed to methods for making arrays of at least 500 compounds in solution phase. All pending claims require that reactants are added to reaction vessels, and the reactants are then reacted in the reaction vessels under solution-phase conditions to form an array of compounds in solution.

In contrast, the Pirrung reference is an abstract that relates to the preparation of 54 carbamate compounds, in "sub-libraries". Pirrung neither teaches nor discloses methods for the generation of solution phase libraries as presently claimed by applicants. Moreover, Pirrung provides no experimental details about the structures of the compounds, nor about the specific methods by which the compounds were made.

The Examiner has cited Pirrung as teaching the solution-phase synthesis of compounds. As described above, Pirrung reference does not describe the method by which the compounds were prepared. The Examiner stated that the compounds of Pirrung are "free form" and that this means that "the compounds are in solution phase." Applicants respectfully submit that even if the compounds of Pirrung are free form, it does not necessarily follow that they must be in solution phase. In addition, the abstract of the Pirrung reference teaches that "to deduce the most active member of the library, it was prepared as 15 sublibraries in which one of the reacting components was fixed." Emphasis added. Thus, applicants submit that Pirrung, unlike the present invention, is not directed to solution phase reactions. Assuming, *arguendo*, that Pirrung does describe the solution-phase synthesis of compounds, Pirrung does not teach or suggest the synthesis of at least 500 different compounds in solution phase (as the Examiner has conceded).

The Examiner states that Gallop, in combination with Pirrung, would enable one of skill in the art to make a 500 compound array. Applicants respectfully traverse this rejection.

Applicants respectfully traverse the above rejection. Gallop is a review article describing combinatorial chemistry technology. The combination of the Gallop and Pirrung references suggested by the Examiner is not apt; in fact, not only would the proposed combination not be obvious, it would not result in the claimed invention.

Applicants submit that the "split synthesis" method described in Gallop (at page 1242 and Figure 2) is not a *solution-phase* synthesis method at all. Instead, the Gallop reference is describing the synthesis of chemical compounds attached to a plurality of *solid-phase* supports (e.g., resin beads). These individual solid-phase support beads, as described by Gallop, can be combined into a single reaction vessel (e.g., for purification of the solid-phase reactants), and then subsequently the supports in one reaction vessel can be "split" or

apportioned among many reaction vessels for subsequent reaction steps. This method is well known, and is well suited for the generation of many compounds bound to solid supports. It is not, however, applicable to solution-phase synthesis, in which the “splitting” of some compounds (but not others) from among a mixture of compounds, would be difficult if not impossible.

Thus, the Examiner is proposing to combine a method known for use in solid-phase synthesis (from Gallop), with what is (apparently) a solution-phase synthesis as described in Pirrung. This combination would be inoperative. An *inoperative* combination of references cannot render obvious the claimed invention. The Federal Circuit has clearly stated that combination of references is improper unless the references themselves provide both a motivation to combine the references, and a reasonable expectation that such a combination would be successful (see, e.g., *In re Dembicza* 175 F.3d 994, 50 USPQ2d 1614). Accordingly, Applicants submit that the claimed invention is not, and cannot be, obvious in light of the cited references, as an inoperative combination cannot provide either motivation to combine or an expectation of success (see, e.g., *Robotic Vision Systems, Inc. v. View Engineering, Inc.*, 189 F.3d 1370, 51 USPQ2d 1948 (Fed. Cir. 1999) “[t]he party seeking a holding of invalidity based on a combination of two or more prior art teachings must show some motivation or suggestion to combine the teachings”).

Moreover, even if the combination of references suggested by the Examiner is not inoperative, one of ordinary skill in the art would not be motivated to combine the references as cited by the Examiner. Gallop does not teach or suggest the solution-phase synthesis of compounds in combinatorial reactions, as claimed. As described above, the “split synthesis” of Gallop is a solid-phase technique, not a solution-phase technique; in contrast, Pirrung appears to describe a synthesis of mixtures of compounds in solution. One of ordinary skill in the art would not be motivated to combine the references cited in the way suggested by the Examiner, to arrive at the claimed invention.

In addition, the skilled artisan could not have a reasonable expectation of success in combining the references in the manner suggested by the Examiner. Applicants respectfully point out that while Gallop does describe a mathematical formula for determining the number of compounds produced by a combinatorial synthesis, and provides the example of 100 million tetrameric entities, Gallop does not provide any solution-phase method by which such large numbers of compounds could be prepared. As described above, the solid-phase methods described by Gallop are not applicable to the solution-phase methods of the present claims. Pirrung itself does not teach or suggest that libraries of at least 500 compounds could be prepared by the (vaguely described) methods of that reference. Gallop

does not support the proposition that the method of Pirrung could be combined with another method, or indeed be modified in any way, to arrive at the claimed invention. The Examiner's unsupported statement that "a combinatorial library of 500 different compounds can be prepared using the formula given by Gallop et al." does not demonstrate any expectation that the methods of the Gallop paper could be modified or combined with the methods of Pirrung in any way; the mathematical formula of the Gallop paper is no more than a means for calculating numbers of compounds; it does not *enable* the synthesis of compounds. Accordingly, there could be no reasonable expectation that such a combination would be successful, and the skilled artisan could not have been motivated to combine the references as suggested by the Examiner.

For at least the above reasons, Applicants submit that the rejections based on Pirrung and Gallop have been overcome and should be withdrawn.

Conclusion

Applicants respectfully submit that the entire application is now in condition for allowance, early notice of which would be appreciated.

No fee is believed to be due for the claim changes of this response. Should any fees be required, please charge them to Pennie & Edmonds LLP deposit account no. 16-1150.

Respectfully submitted,

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